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Blood and Urinary Metal Levels among Exclusive Marijuana Users in NHANES (2005–2018)

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Background: Marijuana is the third most used drug in the world.

Objectives: Because the cannabis plant is a known scavenger of metals, we hypothesized that individuals who use marijuana will have higher metal biomarker levels compared with those who do not use.

Methods: We combined data from the National Health and Nutrition Examination Survey (2005–2018) for $n = 7{,}254$ participants, classified by use: non-marijuana/non-tobacco, exclusive marijuana, exclusive tobacco, and dual marijuana and tobacco use. Five metals were measured in blood and 16 in urine using inductively coupled plasma mass spectrometry; urinary metals were adjusted for urinary creatinine.

Results: Participants reporting exclusive marijuana use compared with non-marijuana/non-tobacco use had statistically significantly higher mean cadmium levels in blood [1.22 μg/L (95% CI: 1.11, 1.34); $p < 0.001$] and urine [1.18 μg/g (95% CI: 1.0, 1.31); $p = 0.004$] and statistically significantly higher mean lead levels in blood [1.27 μg/dL (95% CI: 1.07, 1.50); $p = 0.006$] and urine [1.21 μg/g (95% CI: −0.006, 1.50); $p = 0.058$].

Discussion: Our results suggest marijuana is a source of cadmium and lead exposure. Research regarding cannabis use and cannabis contaminants, particularly metals, should be conducted to address public health concerns related to the growing number of cannabis users. https://doi.org/10.1289/EHP12074

Introduction

Marijuana is the third most commonly used drug in the world behind tobacco and alcohol.[1] As of 2022, 21 states and Washington, DC, covering >50% of the U.S. population, have legalized recreational use of marijuana, and medical marijuana is legal in 38 states and Washington, DC.[2] However, because marijuana is still illegal at the federal level, regulation of contaminants in all cannabis-containing products remains piecemeal and there has been no guidance from federal regulatory agencies such as the U.S. Food and Drug Administration or the U.S. Environmental Protection Agency.[3]

Metal and metalloid (henceforth collectively referred to as metal) contamination of marijuana products occurs during growth, production, and consumption, posing potential harmful effects to end users.[3] The cannabis plant, from which marijuana is derived, is a known hyperaccumulator of metals present in water, soil, fertilizers, and pesticides.[4] Unfiltered marijuana smoke contains high concentrations of metals[5] and vape delivery devices have shown metal leaching in cannabis aerosols.[6] Although 28 states regulate inorganic arsenic (As), cadmium (Cd), lead (Pb), and total mercury (Hg) concentrations in marijuana products, regulation limits vary by metal and by state.[7] Limited data exists for exposure to other metals, such as chromium (Cr), cobalt (Co), and nickel (Ni), that may come from relevant consumption practices.[8] At the limits regulated by the states of California[9] and Colorado[10] (0.2 μg/g As, 0.2 μg/g Cd, 0.5 μg/g Pb, and 0.1 μg/g total Hg in inhalable marijuana products), consumers may be exposed to metal levels that have been shown to be associated with cardiopulmonary diseases,[11–16] neurodevelopmental effects, and cancer.[17,18]

Because marijuana is relatively unregulated in an industry experiencing exponential growth, there is a need to understand contaminant exposures, including metals, associated with marijuana use. As of 2019, 48.2 million people, or 18% of Americans, report using marijuana at least once within the last year.[19] Despite the robust literature on metal biomarker levels among cigarette smokers[20–22] and growing evidence of metal contents in marijuana products,[7,23–25] few studies have reported biomarker metal levels among marijuana users.[26] In 2020, Ngueta et al. reported an association between lifetime use of marijuana with urinary and blood Cd levels in the National Health and Nutrition Examination Survey (NHANES) 2009–2016. Other metals beyond Cd and the contribution of recent marijuana use have not been evaluated in NHANES or other populations. We hypothesized that individuals reporting current marijuana use (either exclusive marijuana or dual tobacco and marijuana use) would have higher levels of biospecimen metals than non-marijuana, non-tobacco users, reflecting internal dose. This secondary data analysis of all measured metals in NHANES, a representative sample of the U.S. population, compared participants' metal levels (5 metals in blood and 16 in urine) by categories of marijuana and tobacco use. Among exclusive marijuana users, we compared metal levels by days since last use.

Methods

Study Population

Led by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC), NHANES is a biannual program of studies designed to assess the health and nutritional status of adults and children in the United States. NHANES is designed as a multiyear, stratified, clustered four-stage sample of noninstitutionalized civilians with fixed sample-size targets for sampling domains defined by age, sex, race and ethnicity, and socioeconomic status, with data released in 2-y cycles. Participants gave informed consent of the survey process and their rights as a participant, and the survey was approved by

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the NCHS Review Board.[27] Questionnaires were administered in-home followed by standardized health examinations in specially equipped mobile examination centers. Publicly available, deidentified, and detailed health data sets are available on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/). We acquired NHANES data from seven 2-y cycles (2005–2018) to create a larger and more geographically diverse sample, including all cycles with available data on blood and urinary metals and detailed drug use.

Exclusion Criteria

Of the 70,190 NHANES participants from the combined 2005–2018 cycles, 10,921 participants had metals measured in blood and urine and available drug use questionnaire data. Individuals ≥18 years of age were included in our analysis. We excluded 2,928 individuals who were missing marijuana use, 337 missing serum cotinine, 335 missing urine As levels, 54 missing body mass index, 9 missing blood metals, and 4 missing urinary creatinine, leaving a total of 7,254 participants (Figure S1).

Blood Metals

As previously described,[28] whole blood specimens were collected at mobile examination centers, frozen at −20°C, and shipped to the CDC's Division of Laboratory Sciences, National Center for Environmental Health (NCEH) for analysis. Prior to analysis, whole blood samples were diluted: 1 part sample +1 part deionized water +48 parts diluent to solubilize blood components and aid aerosol generation for analysis. All metals were measured in whole blood using inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS). Cd, Pb, and total Hg were measured in whole blood for all included NHANES cycles (2005–2017). Manganese (Mn) and selenium (Se) were measured in whole blood starting in 2011 and every cycle thereafter (Table S1). Total Hg was measured only in women of childbearing age and 1- to −5-y-old children. There were no changes in equipment, laboratory methods, or laboratory site in any cycle. Lower limits of detection declined in 2013 but remained steady thereafter (Table S2). Values below the limit of detection (LOD) were imputed, with the lower level of detection (LLOD) divided by the square root of 2. The percentage of participants with metal levels below the LOD are reported in Table S2, and they range between 0% for Pb, Mn, and Se and 12% for Cd and Hg. All blood metals were reported as levels in micrograms of metal per liter of blood, or per deciliter of blood for Pb.

Urinary Metals

As previously described,[29] spot urine specimens were collected at mobile examination centers in metal-free containers, frozen at −20°C, and shipped to the Division of Environmental Health Laboratory Sciences, NCEH, for analysis. ICP-DRC-MS was used to measure the following 15 elements in urine in micrograms per liter: total As, (tAs), antimony (Sb), barium (Ba), beryllium (Be), Cd, Co, cesium (Cs), Pb, Mn, molybdenum (Mo), platinum (Pt), strontium (Sr), thallium (Tl), tin (Sn), tungsten (W), and uranium (U). Urine samples were diluted 1:9 with 2% (vol/vol), double-distilled, concentrated nitric acid containing both iridium and rhodium for multi-internal standardization.[30] tAs, Ba, Cd, Co, Cs, Mo, Pb, Sb, Tl, and W were measured at all NHANES cycles (2005–2017). Data was available at designated cycles for the following metals: Be (2005–2009), Mn (2011–2017), Pt (2005–2009), Sr (2011–2015), Sn (2011–2017), and U (2005–2015). See Table S1. Values below the LOD were imputed, with the LLOD divided by the square root of 2. Be and Pt were excluded from analyses because >90% of the samples were below the LOD (Table S2). For all other metals, the percentage of samples below the LOD ranged from 0% to 61%.

High-performance liquid chromatography (HPLC) coupled to ICP-DRC-MS was used to detect the As species arsenobetaine (Ab), and dimethylarsinic acid (DMA). All As species were measured at each of the NHANES cycles included (Table S2). Urine samples were diluted 1:9 with 2% (vol/vol) double-distilled nitric acid containing gallium or tellurium for internal standardization. Values below the LOD were imputed, with the LLOD divided by the square root of 2. Total As and DMA species were recalibrated to remove the contribution of Ab, an indicator of seafood consumption.[31] We used the recalibrated tAs and DMA as measures of inorganic As and internal dose. All urinary metals and metal species were corrected for urine dilution using individual urinary creatinine and reported as levels in micrograms of metal per gram of creatinine.

Marijuana and Tobacco Use Categorization

We used four NHANES variables to define exclusive marijuana and tobacco use: *a*) current cigarette smoking, *b*) serum cotinine levels, *c*) self-reported ever marijuana use, and *d*) recent marijuana use. Exclusive tobacco use was defined by individuals who either answered "yes" to "Do you now smoke cigarettes?" (SMQ040) or whose serum cotinine levels were >10 ng/mL (LBXCOT).[32] Non-tobacco use was defined by individuals who either answered "no" to now smoking cigarettes or whose serum cotinine levels were ≤10 ng/mL. Reclassification of self-reported smoking status by serum cotinine levels increased the number of smokers from 1,745 to 2,207 (Table S3). Any individuals with missing self-reported smoking status or serum cotinine were removed from analysis. Serum cotinine was measured by an isotope-dilution HPLC/atmospheric pressure chemical ionization tandem MS (ID HPLC-APCI MS/MS) method, as previously described.[33]

Exclusive marijuana use was defined by individuals who had answered "yes" to both "Ever used marijuana or hashish?" (DUQ200) and had used marijuana within the last 30 d, as derived from the variables "Last time used marijuana" (DUQ220Q) and the unit of time at which the individual last used marijuana in days, months, weeks, or years (DUQ220U). Non-marijuana use was defined by individuals who either answered "no" to ever using marijuana or hashish or had not used marijuana in the past 30 d. We categorized individuals into four types of use: *a*) non-marijuana/non-tobacco use (never user of marijuana or former user who had not used marijuana in >30 d and no tobacco use or serum cotinine ≤10 ng/mL), *b*) exclusive marijuana use (current marijuana use who had used within the last 30 d and self-reported not currently smoking cigarettes or serum cotinine levels of ≤10 ng/mL), *c*) exclusive tobacco use (either self-reported current cigarette smoking or serum cotinine level >10 ng/mL who had not used marijuana within the last 30 d), or *d*) dual use (self-reported current marijuana use who had used within the last 30 d and either self-reported current cigarette smoking or had serum cotinine levels of >10 ng/mL). Hereafter, we refer to these categories as non-marijuana/non-tobacco use, exclusive marijuana use, exclusive tobacco use, or dual use (Table S4).

For our analysis on time since last use among exclusive marijuana users, we restricted analyses to exclusive marijuana use, and categorized recent marijuana use into four groups: individuals who had never used marijuana or had not used marijuana in over a year (reference group), and individuals who had exclusively used marijuana within the last 7, 8–30, or 31–365 d (Table S4).

Covariates

Age, sex, race and ethnicity, education, and household income were acquired from self-reported questionnaires on demographic

information. Race and ethnicity was classified as non-Hispanic White, non-Hispanic Black, Mexican American, Other Hispanic, and Other races (including multiple races), based on self-identified race and ethnicity as originally designated by NHANES. "Other races" included all other races, including non-Hispanic Asian individuals and those reporting multiple races. In the NHANES cycles 2011–2014, non-Hispanic Asian individuals were oversampled using a new race and ethnicity variable (RIDRETH3). Because this variable was included only during half of the study period, we used the original race and ethnicity classification (RIDRETH1). Co-exposure to other metal exposures (e.g., diet) may differ by race and ethnicity and was therefore used for adjustment in our models.[34] We reclassified education as less than a high school education, a high school education or General Education Development (GED) equivalent, or more than a high school education. Household income categories were categorized as \$0–\$24,999, \$25,000–\$54,999, \$55,000–\$74,999, and ≥\$75,000. Body mass index (BMI; in kilograms per meter cubed) was measured at the mobile examination center. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),[35,36] which estimates GFR for the specified categories of race, sex, and serum creatinine in micromoles per liter. eGFR is a measure of glomerular function. GFR can influence metal excretion in urine and was therefore used for adjustment in our models.

Statistical Analysis

To evaluate the characteristics of the study population, we compared participant sociodemographic characteristics, self-reported marijuana and tobacco use, and biomarkers of marijuana and tobacco use across categories of marijuana use using analyses of variance, *t*-tests, and χ^2 tests. To estimate the arithmetic mean difference of biomarker metal concentrations by marijuana use, we built generalized linear models with the gamma distribution and log link function for right-skewed metal concentrations. Groups based on recent marijuana and tobacco use as described above were modeled as categorical independent variables, and blood and urine metal levels were modeled as continuous dependent variables. Model adjustments were chosen *a priori* based on literature review of marijuana and metal biomarkers.[3,37–39] Adjustments included age, sex, race and ethnicity, education, eGFR, and NHANES cycle year. We assessed effect modification of the association between exclusive marijuana and or tobacco use with urinary blood and urine metal levels by subgroups of age, sex, and race and ethnicity.

Sensitivity Analyses

We conducted several sensitivity analyses. Owing to the limitations of the drug use questionnaire, among participants reporting exclusive marijuana use, we evaluated frequency of marijuana use as a sensitivity analysis using DUQ219, "When you did use marijuana, how many pipes or joints did you smoke per day?," and DUQ230, "In the last 30 days, how many days did you use marijuana?" We conducted a sensitivity analysis without adjustment for race and ethnicity in our models. Urinary creatinine levels reflect urine dilution and can vary by age, sex, and other characteristics.[40] Although the influence of kidney function on urinary creatinine levels is generally small and urinary creatinine is commonly used to correct urine albumin, a marker of kidney damage for urine dilution, we also conducted a sensitivity analysis without adjustment for urinary creatinine. We removed eGFR from our models to assess any difference in estimates, particularly for blood metals. We further adjusted our models for serum cotinine to determine whether tobacco use, use of an unaccounted-for nicotine product, or secondhand tobacco exposure may be the source of metal exposures. In addition, we assessed the effect of former cigarette smoking on urinary Cd levels by analyzing ever and never cigarette smokers separately where ever cigarette smokers were those who reported smoking at least 100 cigarettes in their lifetime and never cigarette smokers were those who did not (SMQ020). Finally, we conducted sensitivity analyses, further adjusting for seafood consumption using dietary recall or by further adjusting for urinary Ab levels to account for any metal exposure from seafood in the diet.

Combined NHANES survey cycles and weights produced estimates representative of the U.S. civilian noninstitutionalized population at the midpoint of the combined survey period. We constructed new sample weights for the combined cycles (7 cycles, 2005–2018) by multiplying 2-y subsample A weights for environmental chemicals (WTSA2YR) by 1/7 (for 7 NHANES cycles) as described.[41,42] Model estimates are population-weighted arithmetic mean differences with 95% confidence intervals (CIs) compared with the reference group (non-marijuana/non-tobacco use). All central tendency estimates and proportions were population weighted. Data analysis was performed in R (version 3.1.3; R Development Core Team) using the nhanesA,[43] tidyverse,[44] and survey packages[45] to account for the complex survey design and sampling weights.

Results

The characteristics of NHANES participants by marijuana and tobacco use categories are shown in Table 1 (characteristics by recent use among exclusive marijuana users are shown in Table S5). In comparison with non-marijuana/non-tobacco use, participants reporting exclusive marijuana use were on average younger, more likely non-Hispanic White males, and had lower BMI. Exclusive marijuana use was associated with reporting more than a high school education and a higher income, and 40% had reported formerly smoking cigarettes in their lifetime. Of individuals who used neither marijuana nor tobacco currently, 47% had used marijuana in their lifetime. In unadjusted analysis, blood and urinary metals were lower, except for Cd and Hg in blood, and Sr and Tl in urine, in individuals who reported exclusive marijuana use compared with non-marijuana/non-tobacco use (Table 2; Table S6).

In fully adjusted analyses, we found that blood Cd and Pb levels were higher in participants reporting exclusive marijuana use, exclusive tobacco use, and dual use as compared with non-marijuana/non-tobacco use (Figure 1; Table S7). We found 1.22 μg/L (95% CI: 1.11, 1.34; $p < 0.001$) higher blood Cd levels and 1.27 μg/dL (95% CI: 1.07, 1.50; $p = 0.006$) higher blood Pb levels in participants reporting exclusive marijuana use compared with non-marijuana/non-tobacco use when adjusting for age, sex, race and ethnicity, education, and NHANES cycle year. These results were confirmed in urine where exclusive marijuana use was associated with 1.18 μg/g (95% CI: 1.06, 1.31; $p = 0.004$) higher urinary Cd levels and 1.21 μg/g (95% CI: 0.99, 1.50; $p = 0.06$) higher urinary Pb levels compared with non-marijuana/non-tobacco use (Figure 2; Table S8). Exclusive marijuana use was associated with 1.34 μg/L (95% CI: 1.03, 1.73; $p = 0.03$) higher total blood Hg level. We found that exclusive tobacco use was associated with higher blood levels of Cd and Pb; higher urinary levels of Sb, Ba, Cd, Pb, and U; and lower urinary levels of Mo compared with non-marijuana/non-tobacco use. Dual tobacco and marijuana use was also associated with higher blood levels of Cd and Pb and higher urinary levels of Cd, Pb, and U compared with non-marijuana/non-tobacco use.

To assess metal levels by recent marijuana use, we restricted the sample to only those individuals who had used marijuana

Table 1. Participant characteristics across categories of non-marijuana/non-tobacco use ($n = 4{,}666$), exclusive marijuana use ($n = 358$), exclusive tobacco use ($n = 1{,}511$), and dual use ($n = 719$), among 7,254 NHANES participants (2005–2018).

	Non-marijuana/non-tobacco use[a]	Exclusive marijuana use[b]	Exclusive tobacco use[c]	Dual use[d]
Age [y (mean ± SD)]	40.0 ± 11.8	34.9 ± 12.1	39.7 ± 11.2	34.2 ± 11.5
Sex [*N* (%)]				
Female	2,641 (55.3)	168 (42.2)	641 (41.0)	244 (33.8)
Male	2,025 (44.7)	190 (57.8)	870 (59.0)	475 (66.2)
Race/ethnicity [*N* (%)]				
Mexican American	1,017 (12.2)	49 (7.2)	197 (7.6)	53 (4.9)
Other Hispanic	538 (7.2)	36 (5.6)	101 (3.9)	40 (4.2)
Non-Hispanic White	1,633 (62.1)	153 (70.3)	782 (70.9)	325 (65.5)
Non-Hispanic Black	863 (10.4)	83 (11.4)	300 (10.8)	244 (19.7)
Other race, including multi-race	615 (8.0)	37 (5.4)	131 (6.8)	57 (5.6)
Education [*N* (%)]				
<High school diploma	839 (11.4)	28 (6.2)	410 (20.6)	174 (21.8)
High school graduate/GED	831 (18.0)	64 (19.8)	456 (33.1)	222 (34.9)
>High school diploma	2,832 (70.6)	235 (74.0)	609 (46.3)	285 (43.3)
Household income [*N* (%)]				
$0–$24,999	890 (14.4)	74 (16.2)	513 (27.6)	252 (28.9)
$25,000–$54,999	1,419 (29.6)	112 (30.9)	505 (32.7)	253 (37.5)
$55,000–$74,999	598 (14.8)	39 (9.6)	164 (15.1)	70 (12.5)
$75,000–$100,000 or more	1,361 (41.1)	112 (43.2)	234 (24.6)	102 (21.1)
BMI (kg/m^2)	29.3 (7.1)	28.6 (6.7)	28.9 (6.5)	26.6 (6.4)
Serum cotinine (ng/mL)	0.2 (0.7)	0.8 (1.7)	231.0 (175.1)	200.7 (149.8)
Ever smoker [*N* (%)][e]				
Yes	942 (22.6)	114 (40.2)	1,324 (87.9)	628 (90.6)
No	3,724 (77.4)	244 (59.8)	174 (12.1)	81 (9.4)
Current smoker [*N* (%)][f]				
Yes	0.0 (0.0)	0.0 (0.0)	1,175 (75.3)	570 (81.4)
No	4,666 (100)	358 (100)	323 (24.7)	139 (18.6)
Cotinine smoker [*N* (%)][g]				
Yes	0.0 (0.0)	0.0 (0.0)	1,375 (95.0)	671 (94.7)
No	4,666 (100)	358 (100)	77 (5.0)	29 (5.3)
Ever marijuana use [*N* (%)][h]				
Yes	1,816 (47.0)	358 (100.0)	1,023 (74.1)	719 (100.0)
No	(53.0)	(0.0)	(25.9)	(0.0)
Creatinine (mg/dL)	117.3 (77.1)	132.3 (76.3)	132.6 (88.0)	139.1 (90.2)
eGFR (mL/min per 1.73 m^2)	101.0 (19.0)	105.7 (18.0)	100.9 (17.2)	106.0 (17.9)

Note: Analyses conducted using survey package to account for NHANES complex sampling design and weights; percentages are weighted and indicate population percentages. Continuous variables are reported as mean ± SD and categorical variables as number (population-weighted percentage). Note: BMI, body mass index; eGFR, estimated glomerular filtration rate; GED, General Education Development (U.S. high school diploma alternative); NHANES, National Health and Nutrition Examination Survey; SD, standard deviation.

[a]The reference group of non-marijuana/non-tobacco use includes individuals who had not used marijuana within the last 30 d and individuals who self-reported they did not currently smoke cigarettes or those with serum cotinine levels of ≤10 ng/mL ($n = 4{,}666$).

[b]Exclusive marijuana use includes those who had used marijuana within the last 30 d and had serum cotinine levels of <10 ng/mL ($n = 358$).

[c]Exclusive tobacco use includes those who either self-reported currently smoking cigarettes or had a serum cotinine level of >10 ng/mL and had not used marijuana within the last 30 d ($n = 1{,}511$).

[d]Dual use includes both individuals who had used marijuana within the last 30 d and either currently smoked cigarettes or had serum cotinine levels of >10 ng/mL ($n = 719$).

[e]Ever smoker is a participant who self-reported smoking at least 100 cigarettes in their lifetime.

[f]Current smoker is a participant who self-reported currently smoking cigarettes.

[g]Cotinine smoker is a participant with serum cotinine values of >10 μg/L.

[h]Ever cannabis use is a participant who self-reported having ever used marijuana.

within the last year ($n = 569$) and non-marijuana/non-tobacco users ($n = 4{,}455$), excluding exclusive tobacco and dual users (see Tables S5 and S6 for descriptive statistics). In fully adjusted analyses, individuals who had used marijuana within the last 7 d had higher Cd and Pb levels in both blood and urine compared with those who did not use marijuana or had not used marijuana in more than a year. We found 1.23 μg/L (95% CI: 1.12, 1.35; $p < 0.001$) higher Cd and 1.39 μg/dL (95% CI: 1.11, 1.75; $p = 0.005$) higher Pb concentrations in blood among those who had used in the last week as compared with those who do not use marijuana or had not used marijuana within the last year (Figure 3; Table S9). These results were confirmed in urine with 1.20 μg/g (95% CI: 1.03, 1.39; $p = 0.02$) higher Cd and a 1.31 μg/g (95% CI: 1.01, 1.70; $p = 0.045$) higher Pb levels compared with non-marijuana use (Figure 4; Table S10). As time since last use increased, mean Cd and Pb levels in blood and urine were lower. Marijuana use within the last 7 d was associated with 1.40 μg/L (95% CI: 1.06, 1.85; $p = 0.02$) higher total blood Hg level.

In sensitivity analyses, we found that associations for Cd and Pb levels in both urine and blood were higher among individuals >30 years of age (Figures S2 and S3). Exclusive marijuana users who were females had higher blood and urinary Cd levels than males. However, males who used tobacco and reported dual use had higher levels of blood and urinary Cd. Associations for blood and urinary Cd levels were stronger among non-Hispanic White individuals than other race and ethnicity groups (Figures S4 and S5). In addition, we evaluated the frequency of marijuana use among exclusive marijuana users, modeling the number of joints or pipes smoked per day. Consistent with our primary analysis on time since last use among exclusive marijuana users, we found similar patterns for the number of joints or pipes smoked per day. Those who reported using more than three to five joints or pipes per day had had higher levels of blood Cd and those reporting six or more joints or pipes per day had higher levels of blood and urinary Pb (Figures S6 and S7). In addition, we evaluated models without adjustment for race and ethnicity and found little difference in the results (Figures S8–S11). In sensitivity analyses, we

Table 2. Median (interquartile range) metal levels measured in urine (μg/g) and in blood (μg/L or μg/dL for lead) across categories of non-marijuana/non-tobacco ($n = 4,666$), exclusive marijuana use ($n = 358$), exclusive tobacco use ($n = 1,511$), and dual use ($n = 719$), among 7,254 NHANES participants (2005–2018).

Metal	Non-marijuana/non-tobacco use[a]	Exclusive marijuana use[b]	Exclusive tobacco use[c]	Dual use[d]
Urinary metals				
2003 total arsenic[e]	3.82 (2.51–6.09)	3.27 (2.38–5.22)	3.44 (2.35–5.39)	3.34 (2.30–5.26)
DMA[e]	2.62 (1.67–4.23)	2.37 (1.53–3.73)	2.30 (1.51–3.65)	2.21 (1.43–3.36)
Antimony	0.05 (0.03–0.08)	0.05 (0.03–0.07)	0.06 (0.04–0.09)	0.05 (0.04–0.08)
Barium	1.31 (0.75–2.32)	1.22 (0.79–2.14)	1.43 (0.78–2.55)	1.26 (0.70–2.14)
Cadmium	0.15 (0.09–0.26)	0.13 (0.07–0.22)	0.24 (0.11–0.49)	0.18 (0.09–0.38)
Cesium	4.36 (3.21–6.00)	4.05 (3.11–5.52)	3.89 (2.83–5.67)	3.53 (2.59–4.79)
Lead	0.33 (0.21–0.54)	0.30 (0.17–0.49)	0.43 (0.26–0.71)	0.39 (0.27–0.7)
Strontium	97.11 (61.82–145.27)	97.53 (62.07–134.12)	95.27 (59.30–161.11)	95.51 (60.58–136.36)
Thallium	0.16 (0.12–0.23)	0.17 (0.12–0.23)	0.14 (0.10–0.19)	0.13 (0.10–0.19)
Tin	0.41 (0.23–0.79)	0.36 (0.17–0.66)	0.41 (0.23–0.76)	0.37 (0.21–0.74)
Tungsten	0.07 (0.04–0.12)	0.06 (0.04–0.11)	0.07 (0.04–0.11)	0.07 (0.04–0.12)
Uranium	0.005 (0.003–0.009)	0.005 (0.003–0.008)	0.007 (0.004–0.012)	0.006 (0.004–0.010)
Cobalt	0.37 (0.25–0.54)	0.32 (0.22–0.49)	0.33 (0.23–0.50)	0.32 (0.23–0.45)
Manganese	0.13 (0.07–0.22)	0.11 (0.06–0.16)	0.10 (0.06–0.20)	0.10 (0.06–0.19)
Molybdenum	38.71 (26.45–57.01)	36.04 (25.45–47.78)	33.79 (23.84–49.51)	32.34 (20.55–49.59)
Blood metals[f]				
Cadmium	0.22 (0.14–0.31)	0.22 (0.14–0.32)	0.75 (0.34–1.24)	0.76 (0.40–1.25)
Lead[g]	0.82 (0.55–1.30)	0.81 (0.55–1.28)	1.21 (0.76–1.87)	1.25 (0.83–1.91)
Total mercury	0.87 (0.44–1.63)	0.96 (0.48–2.23)	0.68 (0.36–1.34)	0.67 (0.35–1.20)
Manganese	9.42 (7.51–11.71)	8.76 (7.29–10.72)	9.24 (7.36–11.09)	8.70 (7.30–10.71)
Selenium	194.1 (178.9–208.0)	196.6 (181.2–213.6)	193.7 (179.4–209.8)	191.0 (179.2–207.3)

Note: DMA, dimethyl arsenic acid, NHANES, National Health and Nutrition Examination Survey.
[a]The reference group of non-marijuana/non-tobacco use includes individuals who had not used marijuana within the last 30 d and individuals who self-reported they did not currently smoke cigarettes or those with serum cotinine levels of ≤10 ng/mL ($n = 4,666$).
[b]Exclusive marijuana use includes those who had used marijuana within the last 30 d and had serum cotinine levels of <10 ng/mL ($n = 358$).
[c]Exclusive tobacco use includes those who either self-reported currently smoking cigarettes or had a serum cotinine level of >10 ng/mL and had not used marijuana within the last 30 d ($n = 1,511$).
[d]Dual use includes both individuals who had used marijuana within the last 30 d and either currently smoked cigarettes or had serum cotinine levels of >10 ng/mL ($n = 719$).
[e]Total Arsenic and DMA were recalibrated for arsenobetaine to remove exposure from seafood consumption.
[f]Cadmium, manganese, total mercury, lead, and selenium were measured in whole blood (μg/L).
[g]Lead was measured in whole blood and is reported as μg/dL.

used urine metals not accounting for urine dilution using urinary creatinine, and urine metals adjusted for urine creatinine in the model (instead of dividing) and found little to no change in the results (Figures S12 and S13). Similarly, we removed the adjustment for eGFR and found little difference in the results (Figures S14–S17). We added cotinine to our models to assess any potential confounding of tobacco and secondhand smoke exposure. The associations were attenuated only in those who smoked and those reporting dual use, although these results remained significant, with no changes for recent exclusive marijuana use (Figures S18–S21). To further assess potential confounding by former cigarette use, we stratified by self-reported ever/never cigarette use and found that effect estimates among never cigarette smokers were attenuated for urinary metals; however, results remained consistent for blood metals (Figures S22 and S23). Finally, adjustment for potential metal exposures from seafood consumption showed an attenuation for the association between recent exclusive marijuana use and Hg levels (Figures S24–S27).

Discussion

In this nationally representative study of NHANES participants, we found higher levels of Cd and Pb in blood and urine among participants reporting exclusive marijuana use when compared with participants who neither used marijuana nor tobacco. Cd and Pb levels were also higher in exclusive marijuana users who reported using marijuana within the last 7 d, with metal levels being lower with increased time since last use. Cd biomarker levels were higher in exclusive tobacco users compared with exclusive marijuana users, either because of differences in frequency of use or differences in Cd levels in the tobacco and cannabis plants themselves. However, blood and urinary Pb levels among those who exclusively used marijuana and those who exclusively used tobacco were similar. Dual marijuana and tobacco users also had higher levels of Cd and Pb compared with participants who used neither marijuana nor tobacco. Taken together, these observations suggest that marijuana use is an important and underrecognized source of Cd and Pb exposure independent of tobacco use and that chronic marijuana use may contribute to adverse health effects associated with chronic, low-level metal exposure.

One other study assessed blood and urinary Cd levels in individuals who use marijuana in the 2009–2016 NHANES cycles. Ngueta et al. found that marijuana users had higher Cd levels, and that Cd levels were positively associated with increased frequency and duration of marijuana use.[26] Although the work of Ngueta et al. focused on the relationship between lifetime marijuana use and Cd biomarkers, our study was further able to identify differences in metal levels, including but not limited to Cd, with increasing time since last use among individuals who had recently used marijuana. Furthermore, our analysis more stringently defined exclusive marijuana use by removing underlying metal exposures from tobacco use and assessing multiple metals in addition to Cd. Because tobacco is the predominant source of Cd exposure among cigarette smokers,[11] we also evaluated differences in Cd levels stratified by former smoking status, a more robust indicator of past tobacco use than serum cotinine levels. We found that the relationship between exclusive marijuana use and blood Cd levels were the same regardless of former smoking behavior. However, for urinary Cd, the association between exclusive marijuana users and Cd was consistent across smoking status, but it was stronger for former smokers. These sensitivity analyses confirmed blood Cd as a robust, short-term marker of Cd exposure and urinary Cd as a strong, long-term indicator of past cigarette smoking.[46–48] As in our former smoking behavior analysis, urinary Cd was higher among individuals >30 years of age,

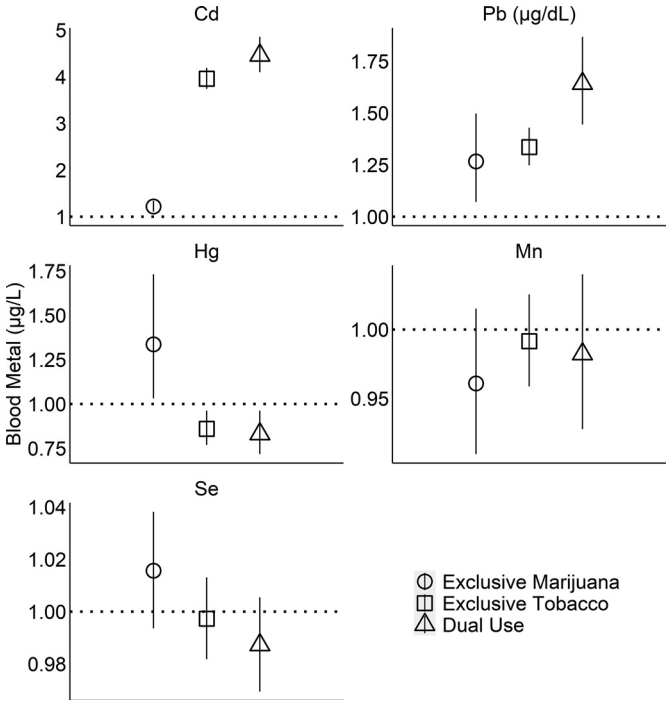

Figure 1. Arithmetic mean differences and 95% CIs in blood metal concentrations (µg/L or µg/dL for Pb) across categories of exclusive marijuana use (circle), exclusive tobacco use (square), and dual use (triangle), as compared with non-marijuana/non-tobacco use (reference), among 7,254 NHANES participants (2005–2018). See Table S7 for all model estimates. The reference group of non-marijuana/non-tobacco use included individuals who had not used marijuana within the last 30 d and individuals who self-reported they did not currently smoke cigarettes or those with serum cotinine levels of ≤10 ng/mL (n = 4,666). Exclusive marijuana use included those who have used marijuana within the last 30 d and had serum cotinine levels of <10 ng/mL (n = 358). Exclusive tobacco use included those who either self-reported currently smoking cigarettes or had a serum cotinine level of >10 ng/mL and had not used marijuana within the last 30 d (n = 1,511). Dual users included both individuals who had used marijuana within the last 30 d and either currently smoked cigarettes or had serum cotinine levels of >10 ng/mL (n = 719). Models were adjusted for age, sex, race, education, eGFR, and NHANES cycle year. Note: Cd, cadmium; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hg, mercury; Mn, manganese; NHANES, National Health and Nutrition Examination Survey; Pb, lead; Se, selenium.

whereas blood Cd was not different between age groups, likely because individuals who used marijuana were younger and thus had a lower body burden of Cd. Females who used marijuana had higher urinary Cd levels compared with males, which has been previously reported and may be explained by differences in divalent metal transporter (DMT1) expression.[49] We did not find clear differences in urinary metal levels by race and ethnicity, with the exception that participants in the "Other races" group had lower levels of metals than those who did not use marijuana. However, associations between marijuana use and blood Cd levels were somewhat stronger among non-Hispanic White participants.

Although urinary Pb levels are reported to be poorly correlated with low levels of environmental exposures,[50] we found that blood and urinary Pb levels were both consistently higher among individuals who exclusively used marijuana compared with nonusers. Pb is a heavy metal known to be detrimental to human health, particularly associated with adverse neurodevelopmental effects in children and cardiovascular disease in adults[17]; health organizations acknowledge that there is no safe level of Pb exposure.[51] Pb is persistent in the environment,[52] and poses potential risks from exposure. Our results indicate that marijuana use was one of these unregulated sources of exposure. Contrary to our study, a recent laboratory-based study of aerosols found no Pb in marijuana smoke.[5] However, the authors reported that the marijuana used in their study was grown in a controlled and contaminant-regulated environment. Thus, our results suggest that not all marijuana is grown in this way and may be contaminated with metals such as Pb. Lower quality fertilizers and irrigation water or soils contaminated with Pb may also contribute to higher Pb levels in the cannabis plant. Finally, a recent study found higher concentrations of Pb in vape aerosols from tobacco/nicotine e-cigarettes, indicating that vaporization may cause metal leaching from vape devices (Ni, Cr, Pb, and zinc), supporting that method of marijuana use may be relevant to our findings.[8] However, method of use was not collected in NHANES, and information concerning metals in cannabis vape aerosols is limited.

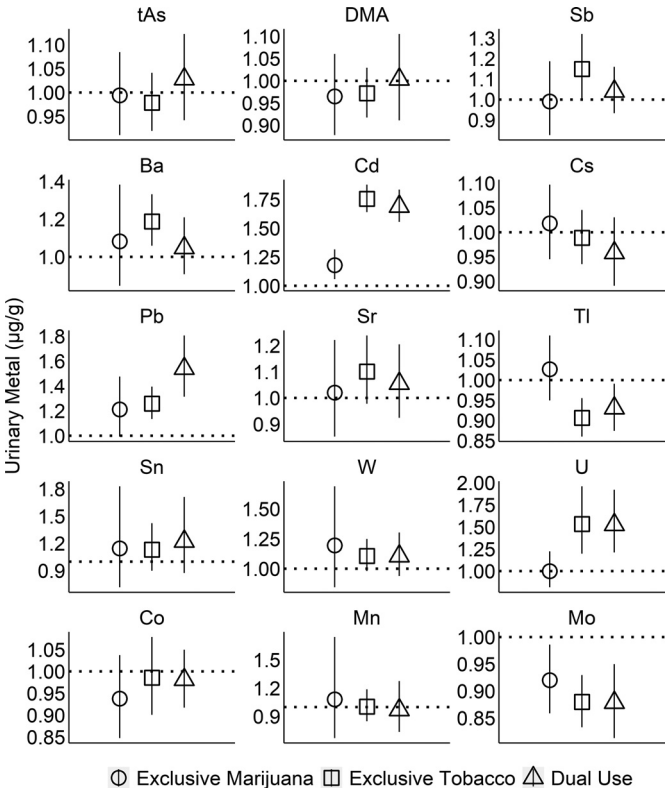

Figure 2. Arithmetic mean differences and 95% CIs in urinary metal levels (µg/g creatinine) across categories of exclusive marijuana use (circle), exclusive tobacco use (square), and dual use (triangle), as compared with non-marijuana/non-tobacco use (reference), among 7,254 NHANES participants (2005–2018). See Table S8 for all model estimates. The reference group of non-marijuana/non-tobacco use included individuals who had not used marijuana within the last 30 d and individuals who self-reported they did not currently smoke cigarettes or those with serum cotinine levels of ≤10 ng/mL (n = 4,666). Exclusive marijuana use included those who had used marijuana within the last 30 d and had serum cotinine levels of <10 ng/mL (n = 358). Exclusive tobacco use included those who either self-reported currently smoking cigarettes or had a serum cotinine level of >10 ng/mL and had not used marijuana within the last 30 d (n = 1,511). Dual users included both individuals who had used marijuana within the last 30 d and either currently smoked cigarettes or had serum cotinine levels of >10 ng/mL (n = 719). Models were adjusted for age, sex, race, education, eGFR, and NHANES cycle year. tAs and DMA were recalibrated for arsenobetaine to remove exposure from seafood consumption. Note: Ba, barium; Cd, cadmium; CI, confidence interval; Co, cobalt; Cs, cesium; DMA, dimethylarsinic acid; eGFR, estimated glomerular filtration rate; Mn, manganese; Mo, molybdenum; NHANES, National Health and Nutrition Examination Survey; Pb, lead; Sb, antimony; Sn, tin; Sr, strontium; tAs, total arsenic; Tl, thallium; U, uranium; W, tungsten.

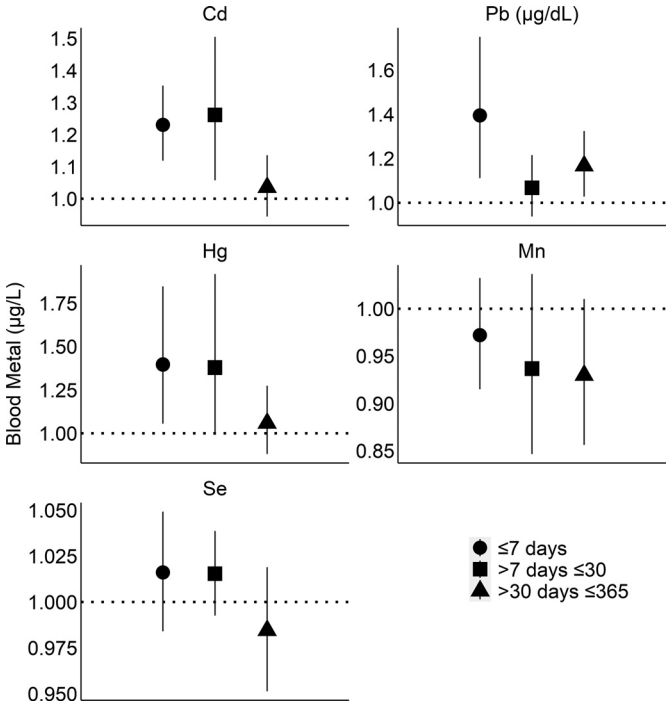

Figure 3. Arithmetic mean differences and 95% CIs in blood metal concentrations (µg/L or µg/dL for Pb) across categories of time since last use among exclusive marijuana users who had used within the last 7 d (circle), the last 8–30 d (square), and the last 31–365 d (triangle), as compared with participants who used neither marijuana nor tobacco or who had not used marijuana in >1 y (reference), $n = 5{,}024$ participants NHANES (2005–2018). See Table S9 for all model estimates. The reference group of nonuse included individuals who used neither marijuana nor tobacco or who had not used marijuana in >1 y ($n = 4{,}455$). Groups of individuals who had recently used marijuana included those who had used within the last 7 d ($n = 226$), those who had used within the last 7–30 d ($n = 132$), or those who had used within the last 31–365 d ($n = 211$). Individuals who self-reported cigarette smoking or had serum cotinine levels of >10 ng/mL were excluded. Models were adjusted for age, sex, race, education, eGFR, and NHANES cycle year. Values of Hg include only women of childbearing age. Note: Cd, cadmium; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hg, mercury; Mn, manganese; NHANES, National Health and Nutrition Examination Survey; Pb, lead; Se, selenium.

Total blood Hg levels were higher among participants reporting exclusive marijuana use and were lower with increasing time since last use. Total blood Hg levels were measured only in women of childbearing age (16–49 years of age) and 1- to 5-y-old children in NHANES; however, individuals <18 years of age were excluded from our analysis. Total blood Hg is a robust measure of short-term total Hg exposure, including inorganic and organic forms.[53] Diet, and in particular, fish consumption, is the primary source of organic Hg exposure in the United States.[54] Our study indicates marijuana may be a source of Hg exposure. However, recent fish consumption may be confounding these results. In our sensitivity analyses, we found that adjusting for seafood consumption did attenuate the estimates for total blood Hg in exclusive marijuana users. Although these estimates were no longer significant, the estimates were still positive.

Tobacco is a documented source of metal exposure.[55] In our study, we found that exclusive tobacco use was associated with higher levels of Sb, Ba, Cd, Pb, W, and U. As in the cannabis plant, Cd and Pb hyperaccumulate in tobacco plants.[56,57] In addition, Cd and Pb are reported to have a high transfer rate from tobacco plant to cigarette smoke (Cd: 81%–90%; Pb 46%–60%) and are found at higher levels in the lung tissue of individuals who smoke cigarettes.[58] Tobacco smoke is the main source of Cd exposure followed by consumption of food for the nonsmoking general population.[59] Tobacco smoking is estimated to increase overall Cd exposure by 15%–30%, although there are discrepancies in reported percentage differences.[60] In our study, we found that exclusive tobacco users had urinary Cd levels (0.75 µg/g) three times higher than those of exclusive marijuana users (0.18 µg/g). Dual users had similarly higher levels of urinary Cd compared with exclusive tobacco users (0.64 µg/g and 0.75 µg/g, respectively). The general population is exposed to Pb from drinking water, food, air and indoor dust.[61] Unlike Cd, tobacco smoke is not the primary source of Pb. However, we found that exclusive tobacco users had 26% higher blood Pb levels than exclusive marijuana users. Dual users, however, had much higher blood Pb levels of 0.64 µg/dL, indicating that cumulative exposures may increase blood Pb levels, as previously reported with Pb from diet.[62,63] Ba has been measured in tobacco plants at high levels (123.0 µg/g), but was reported to have a lower rate of transfer to cigarette smoke.[58,64] Similar to our results, Badea et al. recently found higher levels of Sb and Sr

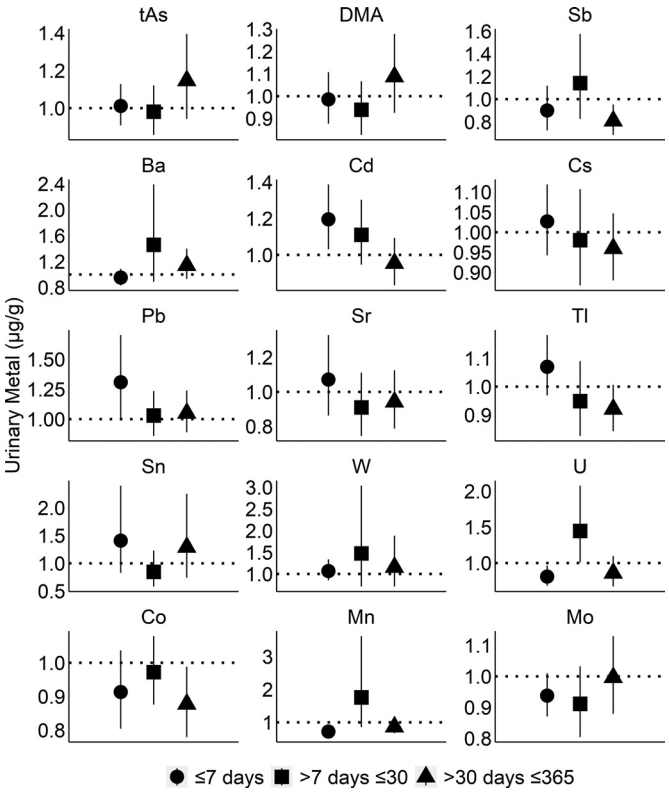

Figure 4. Arithmetic mean differences and 95% CIs in urinary metal levels (µg/g) across categories of time since last use among exclusive marijuana users who had used within the last 7 d (circle), the last 8–30 d (square), and the last 31–365 d (triangle), as compared with participants who used neither marijuana nor tobacco or who had not used marijuana in >1 y (reference), $n = 5{,}024$ participants NHANES (2005–2018). See Table S10 for all model estimates. The reference group of nonuse included individuals who used neither marijuana nor tobacco or who had not used marijuana in >1 y ($n = 4{,}455$). Groups of individuals who had recently used marijuana included those who had used within the last 7 d ($n = 226$), those who had used within the last 8–30 d ($n = 132$), or those who had used within the last 31–365 d ($n = 211$). Individuals who self-reported cigarette smoking or had serum cotinine levels of >10 ng/mL were excluded. Models were adjusted for age, sex, race, education, eGFR, and NHANES cycle year. tAs and DMA were recalibrated for arsenobetaine to remove exposure from seafood consumption. Note: Ba, barium; Cd, cadmium; CI, confidence interval; Co, cobalt; Cs, cesium; DMA, dimethylarsinic acid; eGFR, estimated glomerular filtration rate; Mn, manganese; Mo, molybdenum; NHANES, National Health and Nutrition Examination Survey; Pb, lead; Sb, antimony; Sn, tin; Sr, strontium; tAs, total arsenic; Tl, thallium; U, uranium; W, tungsten.

measured in blood serum of participants recruited from Romania who smoke cigarettes.[65] W and U have been reported as harmful constituents of cigarette smoke,[66] but in an earlier study of NHANES (1999–2004), the authors did not find a significant difference in urinary W levels in participants who did and did not smoke.[67] Thus, our study of NHANES 2005–2018 provides updated evidence of metal exposures from cigarette smoking.

To the best of our knowledge, this is the largest known study on biomarkers of metal exposure in participants who exclusively use marijuana in a representative population of U.S. adults. We combined seven NHANES cycles to include 7,254 participants and evaluated 17 metal biomarkers measured in blood and urine in groups of marijuana use. Previous studies have measured metals in marijuana plants, products, or marijuana smoke; here, we used robust biomarkers of metal exposure and internal dose to explicitly quantify blood and urine metal levels among real-world marijuana users. Our study provides rationale to design cohort studies to investigate metal exposures and their health effects among marijuana users. Finally, we used a stringent definition of marijuana use to include current marijuana use and exclude any current cigarette smokers by self-report and serum cotinine to remove potential confounding by tobacco smoke exposure. Serum cotinine is a short-term marker of tobacco exposure and cannot account for long-term exposure. However, sensitivity analyses adjusted for cotinine and subgroup analysis by former smoking were robust when accounting for potential exposure misclassification from long-term tobacco use.

Limitations of the study include the cross-sectional design, small sample of exclusive marijuana users, recall bias, social desirability bias, and potential for exposure misclassification. Because of the cross-sectional design, we can only estimate associations, not causation, between metal biomarker levels and marijuana use, and thus further work is required to corroborate the findings of our study. Participants in states where marijuana use is legal may be more likely to report marijuana use more accurately than those where marijuana use is still criminalized. Similarly, participants, particularly Black and Hispanic populations, historically targeted for illicit drug use may be disinclined to report marijuana use despite decriminalization, which may explain our small sample of individuals who exclusively used marijuana. Although the landscape of marijuana use is changing rapidly, the NHANES drug use questionnaire did not include method of use, such as vape, combustibles, and edibles, and thus we were unable to determine the difference in metal concentrations by method of use. Data from cohorts such as the Population Assessment of Tobacco and Health[68] or other more contemporary cohorts designed to study cannabis use may help elucidate differences in contaminants by type of marijuana and its origin and methods of use, particularly products growing in popularity, such as cannabis vape, consumables, and use of cannabidiol (CBD) oil. The combination of analytical chemistry analysis, *in vitro* and *in vivo* experiments, and epidemiological research will ultimately be needed to adequately answer how the use of marijuana products contributes to metal exposure and the resulting health effects in the U.S. population. Our results highlight the need to design contemporary studies to examine real-world marijuana use and related exposures in the rapidly growing marijuana industry.

We found overall associations between internal metal levels and exclusive marijuana use, highlighting the relevance of marijuana for metal exposure and the importance of follow-up studies to identify the long-term implications of these exposures. Future investigations of cannabis contaminants must assess other contaminants of concern and potential health effects to inform regulatory, industry and other key stakeholders, to safeguard public health and address safety concerns related to the growing use of cannabis in the United States.

Acknowledgments

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References

1. United Nations Office on Drugs and Crime. 2021. *World Drug Report 2021. Global Overview: Drug Demand and Supply*. United Nations publication, Sales No. E.21. XI.8. New York, NY: United Nations Office on Drugs and Crime. https://www.unodc.org/res/wdr2021/field/WDR21_Booklet_2.pdf [accessed 1 July 2022].
2. Ballotpedia. 2023. Marijuana laws and ballot measures in the United States. https://ballotpedia.org/Marijuana_laws_and_ballot_measures_in_the_United_States [accessed 1 June 2022].
3. Seltenrich N. 2019. Cannabis contaminants: regulating solvents, microbes, and metals in legal weed. Environ Health Perspect 127(8):082001, PMID: 31430176, https://doi.org/10.1289/EHP5785.
4. Bengyella L, Kuddus M, Mukherjee P, Fonmboh DJ, Kaminski JE. 2021. Global impact of trace non-essential heavy metal contaminants in industrial cannabis bioeconomy. Toxin Rev 41(4):1215–1225, https://doi.org/10.1080/15569543.2021.1992444.
5. Moir D, Rickert WS, Levasseur G, Larose Y, Maertens R, White P, et al. 2008. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol 21(2):494–502, PMID: 18062674, https://doi.org/10.1021/tx700275p.
6. Mallampati SR, McDaniel C, Wise AR. 2021. Strategies for nonpolar aerosol collection and heavy metals analysis of inhaled cannabis products. ACS Omega 6(26):17126–17135, PMID: 34250369, https://doi.org/10.1021/acsomega.1c02740.
7. Jameson LE, Conrow KD, Pinkhasova DV, Boulanger HL, Ha H, Jourabchian N, et al. 2022. Comparison of state-level regulations for cannabis contaminants and implications for public health. Environ Health Perspect 130(9):097001, PMID: 36102653, https://doi.org/10.1289/EHP11206.
8. Olmedo P, Goessler W, Tanda S, Grau-Perez M, Jarmul S, Aherrera A, et al. 2018. Metal concentrations in e-cigarette liquid and aerosol samples: the contribution of metallic coils. Environ Health Perspect 126(2):027010, PMID: 29467105, https://doi.org/10.1289/EHP2175.
9. California Bureau of Cannabis Control. 2023. California Code of Regulations. Text of Regulations. https://www.bcc.ca.gov/law_regs/cannabis_order_of_adoption.pdf [accessed 1 July 2022].
10. Colorado Secretary of State. 2023. Code of Colorado Regulations. Colorado Marijuana Rules. Denver, CO: Colorado Secretary of State. https://www.sos.state.co.us/CCR/DisplayRule.do?action=ruleinfo&ruleId=3314 [accessed 1 June 2022].
11. Navas-Acien A, Selvin E, Sharrett AR, Calderon-Aranda E, Silbergeld E, Guallar E. 2004. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. Circulation 109(25):3196–3201, PMID: 15184277, https://doi.org/10.1161/01.CIR.0000130848.18636.B2.
12. Navas-Acien A, Silbergeld EK, Sharrett R, Calderon-Aranda E, Selvin E, Guallar E. 2005. Metals in urine and peripheral arterial disease. Environ Health Perspect 113(2):164–169, PMID: 15687053, https://doi.org/10.1289/ehp.7329.
13. Ruiz-Hernandez A, Navas-Acien A, Pastor-Barriuso R, Crainiceanu CM, Redon J, Guallar E, et al. 2017. Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988–2004. Int J Epidemiol 46(6):1903–1912, PMID: 29025072, https://doi.org/10.1093/ije/dyx176.
14. Nigra AE, Ruiz-Hernandez A, Redon J, Navas-Acien A, Tellez-Plaza M. 2016. Environmental metals and cardiovascular disease in adults: a systematic review beyond lead and cadmium. Curr Environ Health Rep 3(4):416–433, PMID: 27783356, https://doi.org/10.1007/s40572-016-0117-9.
15. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. 2012. Heavy metal toxicity and the environment. Exp Suppl 101:133–164, PMID: 22945569, https://doi.org/10.1007/978-3-7643-8340-4_6.
16. Duffus JH. 2002. "Heavy metals" a meaningless term? (IUPAC technical report). Pure Appl Chem 74(5):793–807, https://doi.org/10.1351/pac200274050793.
17. Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. 2007. Lead exposure and cardiovascular disease—a systematic review. Environ Health Perspect 115(3):472–482, PMID: 17431501, https://doi.org/10.1289/ehp.9785.
18. Argos M, Ahsan H, Graziano JH. 2012. Arsenic and human health: epidemiologic progress and public health implications. Rev Environ Health 27(4):191–195, PMID: 22962196, https://doi.org/10.1515/reveh-2012-0021.

19. CDC (Centers for Disease Control and Prevention). 2021. *Marijuana and Public Health*. Atlanta, GA: CDC. https://www.cdc.gov/marijuana/index.htm [accessed 1 June 2022].
20. Satarug S, Moore MR. 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ Health Perspect 112(10):1099–1103, PMID: 15238284, https://doi.org/10.1289/ehp.6751.
21. Bernhard D, Rossmann A, Wick G. 2005. Metals in cigarette smoke. IUBMB Life 57(12):805–809, PMID: 16393783, https://doi.org/10.1080/15216540500459667.
22. Caruso RV, O'Connor RJ, Stephens WE, Cummings KM, Fong GT. 2013. Toxic metal concentrations in cigarettes obtained from U.S. smokers in 2009: results from the International Tobacco Control (ITC) United States survey cohort. Int J Environ Res Public Health 11(1):202–217, PMID: 24452255, https://doi.org/10.3390/ijerph110100202.
23. Douvris C, Bentil E, Ayensu I, Osei Akoto C, Amponsah IK, Adu J, et al. 2022. Trace metals in cannabis seized by law enforcement in Ghana and multivariate analysis to distinguish among different cannabis farms. Toxics 10(10):567, PMID: 36287847, https://doi.org/10.3390/toxics10100567.
24. Dupree TB, Assen AD, Janusson E, Wise AR, Swider JM, Roggen M. 2023. Simulations of test reduction using pooled heavy metals analysis in cannabis. J AOAC Int 106(2):484–489, PMID: 36331387, https://doi.org/10.1093/jaoacint/qsac140.
25. Gardener H, Wallin C, Bowen J. 2022. Heavy metal and phthalate contamination and labeling integrity in a large sample of US commercially available cannabidiol (CBD) products. Sci Total Environ 851(pt 1):158110, PMID: 35987236, https://doi.org/10.1016/j.scitotenv.2022.158110.
26. Ngueta G, Ndjaboue R. 2020. Lifetime marijuana use in relation to cadmium body burden of US adults: results from the National Health and Nutrition Examination Surveys, 2009–2016. Public Health 187:77–83, PMID: 32927293, https://doi.org/10.1016/j.puhe.2020.08.001.
27. DHHS (U.S. Department of Health and Human Services). 2013. *National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010*. Washington, DC: DHHS. https://www.cdc.gov/nchs/data/series/sr_01/sr01_056.pdf [accessed 1 July 2022].
28. CDC, NCHS (National Center for Health Statistics). 2015. *National Health and Nutrition Examination Survey Laboratory Protocol Blood Multi-Element Analysis by ICP-DRC-MS*. Method number: DLS 3016.8-05. Hyattsville, MD: U.S. Department of Health and Human Services, CDC. https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/labmethods/PBCD-J-PBY-J-R-MET-508.pdf [accessed 1 July 2022].
29. CDC, NCHS. 2015. *National Health and Nutrition Examination Survey Laboratory Protocol Urine Multi-Element ICP-DRC-MS*. Method number: 3018.6-01 (15 element panel) and 3018A.4-01 (total arsenic). Hyattsville, MD: U.S. Department of Health and Human Services, CDC. https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/labmethods/UM-J-MET-508.pdf [accessed 1 July 2022].
30. Mulligan KJ, Davidson TM, Caruso JA. 1990. Feasibility of the direct analysis of urine by inductively coupled argon plasma mass spectrometry for biological monitoring of exposure to metals. J Anal At Spectrom 5(4):301–306, https://doi.org/10.1039/ja9900500301.
31. Jones MR, Tellez-Plaza M, Vaidya D, Grau M, Francesconi KA, Goessler W, et al. 2016. Estimation of inorganic arsenic exposure in populations with frequent seafood intake: evidence from MESA and NHANES. Am J Epidemiol 184(8):590–602, PMID: 27702745, https://doi.org/10.1093/aje/kww097.
32. Kim S. 2016. Overview of cotinine cutoff values for smoking status classification. Int J Environ Res Public Health 13(12):1236, PMID: 27983665, https://doi.org/10.3390/ijerph13121236.
33. CDC. 2022. National Health and Nutrition Examination Survey 2013–2014 Data Documentation, Codebook, and Frequencies. Cotinine and Hydroxycotinine—Serum (COT_H). https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/COT_H.htm [accessed 1 June 2022].
34. Geron M, Cowell W, Amarasiriwardena C, Andra SS, Carroll K, Kloog I, et al. 2022. Racial/ethnic and neighborhood disparities in metals exposure during pregnancy in the northeastern United States. Sci Total Environ 820:153249, PMID: 35065119, https://doi.org/10.1016/j.scitotenv.2022.153249.
35. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. 2006. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145(4):247–254, PMID: 16908915, https://doi.org/10.7326/0003-4819-145-4-200608150-00004.
36. NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases). 2022. Recommended eGFR Calculators. https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/recommended [accessed 21 July 2021].
37. DHHS (U.S. Department of Health and Human Services), Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. 2018. *National Survey on Drug Use and Health 2016*. NSDUH-2016-DS0001. Washington, DC: DHHS. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHMethodsSummDefs2018/NSDUHMethodsSummDefs2018.htm [accessed 1 August 2023].
38. Carliner H, Mauro PM, Brown QL, Shmulewitz D, Rahim-Juwel R, Sarvet AL, et al. 2017. The widening gender gap in marijuana use prevalence in the U.S. during a period of economic change, 2002–2014. Drug Alcohol Depend 170:51–58, PMID: 27875801, https://doi.org/10.1016/j.drugalcdep.2016.10.042.
39. Martins SS, Segura LE, Levy NS, Mauro PM, Mauro CM, Philbin MM, et al. 2021. Racial and ethnic differences in cannabis use following legalization in US states with medical cannabis laws. JAMA Netw Open 4(9):e2127002, PMID: 34570205, https://doi.org/10.1001/jamanetworkopen.2021.27002.
40. O'Brien KM, Upson K, Cook NR, Weinberg CR. 2016. Environmental chemicals in urine and blood: improving methods for creatinine and lipid adjustment. Environ Health Perspect 124(2):220–227, PMID: 26219104, https://doi.org/10.1289/ehp.1509693.
41. Heeringa SG, West BT, Berglund PA. 2017. *Applied Survey Data Analysis*: 2nd ed. New York, NY: Chapman and Hall/CRC Press.
42. CDC, NCHS. Module 3: weighting. https://wwwn.cdc.gov/nchs/nhanes/tutorials/weighting.aspx [accessed 1 August 2022].
43. Endres CJ. 2019. nhanesA: NHANES Data Retrieval. Version 0.6.5.2 ed. https://cran.r-project.org/web/packages/nhanesA/index.html [accessed 1 July 2022].
44. Wickham H, Averick M, Bryan J, Chang W, McGowan LD, François R, et al. 2019. Welcome to the Tidyverse. J Open Source Softw 4(43):1686, https://doi.org/10.21105/joss.01686.
45. Lumley T. 2010. *Complex Surveys: A Guide to Analysis Using R*. Hoboken, NJ: Wiley.
46. Navas-Acien A, Tellez-Plaza M. 2022. Metals and health: science and practice. In: *Maxcy-Rosenau-Last Public Health & Preventive Medicine, 16e*. Boulton ML, Wallace RB, eds. New York, NY: McGraw Hill.
47. Hsieh CY, Wang SL, Fadrowski JJ, Navas-Acien A, Kuo CC. 2019. Urinary concentration correction methods for arsenic, cadmium, and mercury: a systematic review of practice-based evidence. Curr Environ Health Rep 6(3):188–199, PMID: 31372861, https://doi.org/10.1007/s40572-019-00242-8.
48. Vacchi-Suzzi C, Kruse D, Harrington J, Levine K, Meliker JR. 2016. Is urinary cadmium a biomarker of long-term exposure in humans? A review. Curr Environ Health Rep 3(4):450–458, PMID: 27696280, https://doi.org/10.1007/s40572-016-0107-y.
49. Yu HT, Zhen J, Leng JY, Cai L, Ji HL, Keller BB. 2021. Zinc as a countermeasure for cadmium toxicity. Acta Pharmacol Sin 42(3):340–346, PMID: 32284539, https://doi.org/10.1038/s41401-020-0396-4.
50. Sommar JN, Hedmer M, Lundh T, Nilsson L, Skerfving S, Bergdahl IA. 2014. Investigation of lead concentrations in whole blood, plasma and urine as biomarkers for biological monitoring of lead exposure. J Expo Sci Environ Epidemiol 24(1):51–57, PMID: 23443239, https://doi.org/10.1038/jes.2013.4.
51. WHO (World Health Organization). 2022. Lead poisoning. https://www.who.int/news-room/fact-sheets/detail/lead-poisoning-and-health#:~:text=There%20is%20no%20known%20safe,symptoms%20and%20effects%20also%20increase [accessed 25 February 2022].
52. U.S. EPA (U.S. Environmental Protection Agency). 2022. Basic information about lead air pollution. https://www.epa.gov/lead-air-pollution/basic-information-about-lead-air-pollution#:~:text=Lead%20is%20persistent%20in%20the,to%20water%20bodies%20and%20mining [accessed 9 May 2022].
53. Cherian MG, Hursh JB, Clarkson TW, Allen J. 1978. Radioactive mercury distribution in biological fluids and excretion in human subjects after inhalation of mercury vapor. Arch Environ Health 33(3):109–114, PMID: 686833, https://doi.org/10.1080/00039896.1978.10667318.
54. Ye BJ, Kim BG, Jeon MJ, Kim SY, Kim HC, Jang TW, et al. 2016. Evaluation of mercury exposure level, clinical diagnosis and treatment for mercury intoxication. Ann Occup Environ Med 28:5, PMID: 26807265, https://doi.org/10.1186/s40557-015-0086-8.
55. Navas-Acien A. 2018. Global tobacco use: old and new products. Ann Am Thorac Soc 15(suppl 2):S69–S75, PMID: 29676648, https://doi.org/10.1513/AnnalsATS.201711-874MG.
56. Liu H, Wang H, Zhang Y, Wang H, Yang J, Liu J, et al. 2019. Comparison of heavy metal accumulation and cadmium phytoextraction rates among ten leading tobacco (*Nicotiana tabacum* L.) cultivars in China. Int J Phytoremediation 21(7):699–706, PMID: 30656970, https://doi.org/10.1080/15226514.2018.1556589.
57. Pasricha S, Mathur V, Garg A, Lenka S, Verma K, Agarwal S. 2021. Molecular mechanisms underlying heavy metal uptake, translocation and tolerance in hyperaccumulators—an analysis: heavy metal tolerance in hyperaccumulators. Environ Chall (Amst) 4:100197, https://doi.org/10.1016/j.envc.2021.100197.
58. Pinto E, Cruz M, Ramos P, Santos A, Almeida A. 2017. Metals transfer from tobacco to cigarette smoke: evidences in smokers' lung tissue. J Hazard Mater 325:31–35, PMID: 27914289, https://doi.org/10.1016/j.jhazmat.2016.11.069.
59. EFSA Panel on Contaminants in the Food Chain. 2011. Statement on tolerable weekly intake for cadmium. EFSA J 9(2):1975, https://doi.org/10.2903/j.efsa.2011.1975.

60. Richter P, Faroon O, Pappas RS. 2017. Cadmium and cadmium/zinc ratios and tobacco-related morbidities. Int J Environ Res Public Health 14(10):1154, PMID: 28961214, https://doi.org/10.3390/ijerph14101154.
61. Abadin H, Ashizawa A, Llados F, Stevens YW. 2007. *Toxicological Profile for Lead*. Atlanta, GA: Agency for Toxic Substances and Disease Registry.
62. Flannery BM, Dolan LC, Hoffman-Pennesi D, Gavelek A, Jones OE, Kanwal R, et al. 2020. U.S. Food and Drug Administration's interim reference levels for dietary lead exposure in children and women of childbearing age. Regul Toxicol Pharmacol 110:104516, PMID: 31707132, https://doi.org/10.1016/j.yrtph.2019.104516.
63. Flannery BM, Middleton KB. 2022. Updated interim reference levels for dietary lead to support FDA's Closer to Zero action plan. Regul Toxicol Pharmacol 133:105202, PMID: 35690180, https://doi.org/10.1016/j.yrtph.2022.105202.
64. Chiba M, Masironi R. 1992. Toxic and trace elements in tobacco and tobacco smoke. Bull World Health Organ 70(2):269–275, PMID: 1600587.
65. Badea M, Luzardo OP, González-Antuña A, Zumbado M, Rogozea L, Floroian L, et al. 2018. Body burden of toxic metals and rare earth elements in non-smokers, cigarette smokers and electronic cigarette users. Environ Res 166:269–275, PMID: 29908458, https://doi.org/10.1016/j.envres.2018.06.007.
66. FDA (U.S. Food and Drug Administration). 2012. Harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Docket No. FDA-2012-N-0143. Fed Reg 77(64):20034–20037. https://www.govinfo.gov/content/pkg/FR-2012-04-03/pdf/2012-7727.pdf [accessed 1 August 2022].
67. Richter PA, Bishop EE, Wang J, Swahn MH. 2009. Tobacco smoke exposure and levels of urinary metals in the U.S. youth and adult population: the National Health and Nutrition Examination Survey (NHANES) 1999–2004. Int J Environ Res Public Health 6(7):1930–1946, PMID: 19742163, https://doi.org/10.3390/ijerph6071930.
68. Hyland A, Ambrose BK, Conway KP, Borek N, Lambert E, Carusi C, et al. 2017. Design and methods of the Population Assessment of Tobacco and Health (PATH) Study. Tobacco Control 26(4):371–378, PMID: 27507901, https://doi.org/10.1136/tobaccocontrol-2016-052934.